Hexameric chiral α-amino lithium alkoxides: a solid-state and theoretical structural investigation

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The nucleophilic reagents lithium *N*-methylpiperazide, **1**-Li, and lithium *N*,*N*,*N*′-trimethylethylenediamide, **2**-Li, react with 1 equiv. of 4-methoxybenzaldehyde and 2-methylbenzaldehyde respectively to afford the corresponding chiral α-amino lithium alkoxides, $(\mathbf{3})_6 \cdot 2\mathrm{PhMe} \cdot \mathrm{THF}$ and $(\mathbf{4})_6 \cdot 2\mathrm{PhMe}$, which are hexamers in the solid state. Stabilisation of the metal centres is assisted by dative coordination of the dialkylamine α-*N*-centres. While for $(\mathbf{3})_6 \cdot 2\mathrm{PhMe} \cdot \mathrm{THF}$ this is rationalised in terms of steric constraints imposed by the employment of a heterocyclic dialkylamine, for $(\mathbf{4})_6 \cdot 2\mathrm{PhMe}$ it contrasts starkly with previously observed structural analogues. *Ab initio* MO calculations are employed to investigate the relationship between structure and ligand chirality.

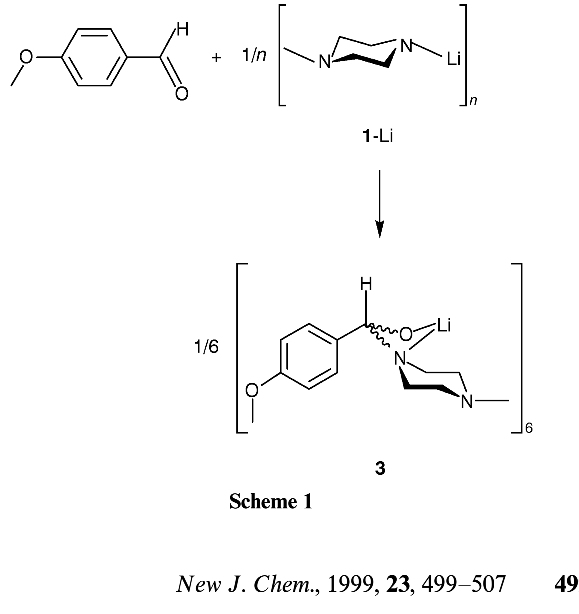
Introduction

While we have reported the synthesis and isolation of a stable derivative of benzonitrile[1] which utilised the metallo-organic nucleophilic reagent lithium *N*,*N*,*N*′-trimethylethylenediamide, **2**-Li, we have more recently employed this auxilliary in studying the regiospecific metallation of aromatic systems,[2] specifically in the context of the lithiation of arylaldehydes.[3] It has been reported previously that the reaction of a lithium dialkylamide with either an arylaldehyde heterocycle[4] or a substituted benzaldehyde[3,5] not only generates an intermediate which contains a good aldehyde protecting group, but also that the dialkylamine moiety itself is capable of directing a further equivalent of lithium to the *ortho*-ring position. The structural natures of such intermediates have, however, been the subject of only a limited number of solution,[6,7] solid-state[6] and theoretical investigations.[8] Such work prompted us to investigate chiral α-amino lithium alkoxides in order to establish in the first instance the coordinative modes adopted by the metal centres in the presence of the intramolecular amine α- and δ-*N*-centres. This has led to reports both of mixed α- and δ-*N*-coordinating tetramers[9] and of a unique, exclusively δ-*N*-stabilised mixed tetranuclear aggregate.[10] We report here the isolation and characterisation of exclusively α-*N*-stabilised α-amino lithium alkoxide hexamers and the rationalisation of their structures by extensive calculational study.[11]

Results and discussion

Solid-state study

While it has been reported[9b] that the potentially bidentate lithium *N*,*N*,*N*′-trimethylethylenediamide (**2**-Li) reacts with 4-methoxybenzaldehyde to afford a novel tetramer based on a ‘partly-open’ pseudo-cubane motif, it is found here that the employment of a *necessarily mono-coordinating* lithium amide leads to the isolation of a higher aggregation state product. Thus lithium *N*-methylpiperazide (**1**-Li), generated *in situ* by the action of Bu^{n}Li on *N*-methylpiperazine, affords $(\mathbf{3})_6 \cdot 2\mathrm{PhMe} \cdot \mathrm{THF}$ upon treatment with 4-methoxybenzaldehyde (Scheme 1). X-ray crystallography shows this species to be a solid-state hexamer [Fig. 1(a)]. Just as the previously reported *tetrameric* α-amino lithium alkoxides[9] were the first of *their* kind, so too, *hexameric* $(\mathbf{3})_6 \cdot 2\mathrm{PhMe} \cdot \mathrm{THF}$ is the first of its kind, in spite of previous reports of related lithium–oxygen hexamers such as enolates[12] azaenolates,[13] an alkoxide,[14] a phenolate[15] and, most recently, a hydroxylamide.[11] The hexagonal prismatic core observed here comprises two stacked $(\mathrm{OLi})_3$ rings, both of which deviate significantly from planarity [internal angles sum to 707.3°]. While the aggregate core [Fig. 1(b)] appears superficially to have threefold symmetry, the inter-ring distance is, in fact, somewhat variable, with two inter-ring bonds, Li(2)–O(6) 1.881(4) Å [at either ‘end’ of the stack as drawn in Fig. 1b)] being slightly shorter than the remaining four inter-ring bonds (1.894 Å mean). The Li–O bonds within either trimeric ring alternate between ‘long’ (2.039 Å mean) and ‘short’ (1.887 Å mean), with the ‘long’ bonds in the upper ring eclipsing the ‘short’ bonds in the lower one. The three organic residues on each ring are orientated in an approximately equivalent fashion, with all three protected aldehyde hydrogen atoms adopting an *endo*-orientation with respect to the six-membered $(\mathrm{OLi})_3$ ring with which they are associated. This causes the aggregate as a



Scheme 1

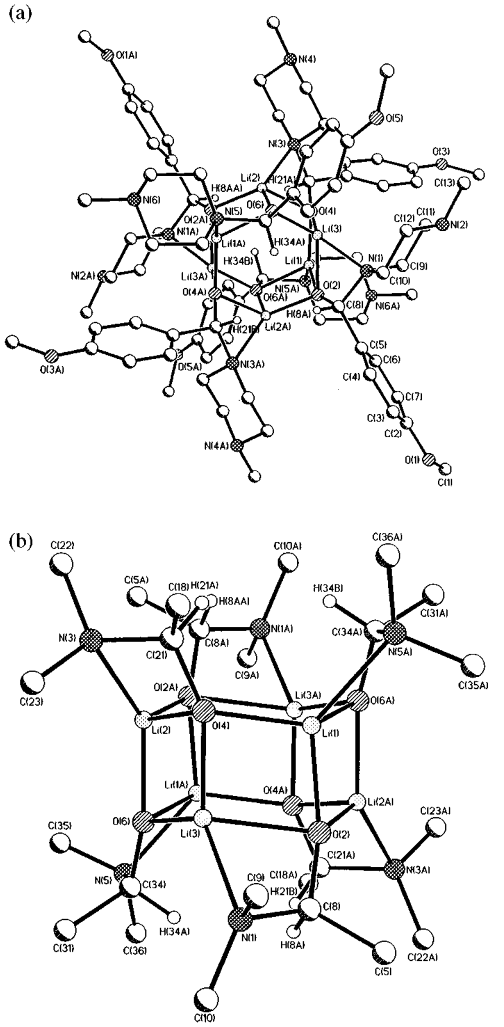


Fig. 1 (a) Molecular structure of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$; hydrogen atoms (except the protected aldehyde hydrogen atoms) and lattice toluene and THF molecules have been omitted for clarity. (b) The $(\text{LiO})_6$ core of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$, showing (top to bottom) the three (*R*)-stereocentres and the three (*S*)-ones.

whole to be racemic, although each $(\text{OLi})_3$ ring is enantiomerically pure.

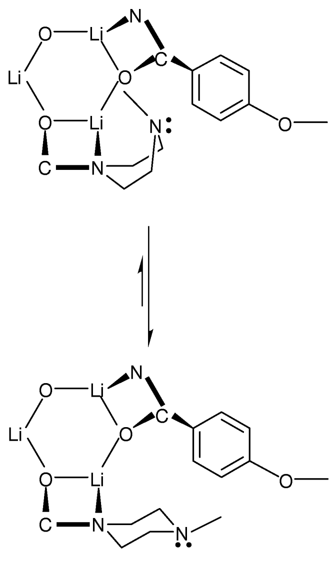
It is noteworthy that $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$, for each hexameric unit of which there are two molecules of lattice toluene and one of lattice THF in the unit cell, is isolable as an unsolvated hexamer not only from THF, but also from PMDETA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine). This contrasts with the hexameric lithium azaenolate, lithium *N*-isopropylbenzamide,[13] wherein three different amide units are observed, two showing intramolecular α-N–Li coordination, the third incorporating THF at the expense of this interaction. The α-N–Li bond lengths in $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$ appear to vary according to inter-ring O–Li distance. While the shortest such distance [N(1)–Li(3) 2.131(4) Å] is associated with the monomers whose charged alkoxide centres (*i.e.* Li^+ or O^-) do not represent the points of closest approach of the two trimeric rings, the monomers which lend an atom to these points of closest approach show longer α-N–Li interactions [N(5)–Li(1A) and N(3)–Li(2) = 2.147(4) and 2.154(4) Å, respectively]. These distances are all somewhat longer than those in the four- and five-membered Li–N chelates observed in the hexameric lithium azaenolate, lithium *N*-isopropylbenzamide (1.85 and 2.03 Å)[13] and the lithium enolate, lithium *N*,*N*-diethylglycinate, $\text{Li}_6[\text{OC(OEt)}{=}\text{C(H)NEt}_2]_6$ (2.122 Å mean)[12b], respectively. Perhaps more surprisingly though, they are also slightly lengthened compared with the *three*-membered Li–N chelates recorded lately in hexameric lithium dibenzylhydroxylamide (2.131 Å mean).[11]

The contrasting structures of *tetrameric* lithium (*N*,*N*,*N*′-trimethylethylenediamino)(4-methoxyphenyl)methoxide[9] and *hexameric* $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$ suggest a relationship between structure and the availability of the δ-N-centre lone pair for donation to the metal. While in the former aggregate, flexibility in the dialkylamine backbone facilitated bis-coordination of α- and δ-N-centres, the employment of the (less flexible) N-methylpiperazine heterocycle, which can adopt just two conformations (chair and boat), might appear in itself to be responsible for this change in coordinative mode of the dialkylamine. The steric unfavourability of the boat-dialkylamine is demonstrated in Scheme 2, wherein the δ-N-methyl group projects significantly towards the protected aldehyde O-centre of an adjacent monomer in the $(\text{OLi})_3$ ring and, more curiously, the δ-N-centre lone-pair points *away* from the metal centre. This lone-pair orientation, clearly observed in the solid-state structure of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$, is presumably symptomatic of the *anti*-conformation of the lone pairs in the (dominant)[16] lithium *N*-methylpiperazide chair. The structure of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$ suggests, therefore, that during formation of the α-amino lithium alkoxide the α-N-centre of the lithium amide precursor attacks by utilising the electron pair in the polar N–Li bond [Scheme 3(a)] rather than *via* the N-centre lone-pair [Scheme 3(b)].

Surprisingly, bearing in mind the observed tetrameric structure of lithum (*N*,*N*,*N*′-trimethylethylenediamino)(4-methoxyphenyl)methoxide,[9] the hexameric core observed for $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$ can be replicated by the 1 : 1 treatment of **2**-Li with 2-methylbenzaldehyde (Scheme 4). The product, $(\mathbf{4})_6 \cdot 2\text{PhMe}$ [Fig. 2(a) and (b)], in which each hexameric unit is accompanied by two molecules of lattice toluene, is the precursor to the 2-lithiomethylbenzaldehyde synthon.[17] The solid-state structure suffers from a high *R*1 value of 0.1063, resulting from disorder both in the lattice solvent molecules and in the dialkylamine backbones (see Experimental section). This does, however, not negate the fact that there is a hexameric core.

The two stacked $(\text{OLi})_3$ rings observed in the solid-state hexamer show many similarities with those observed in $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$, both rings, comprising alternating lithium and oxygen centres, deviating substantially from planarity (internal angles sum to 712.3°) and showing alternating 'long' (1.987 Å mean) and 'short' (1.871 Å mean) Li–O bonds arranged within either trimeric ring such that the the 'long' bonds in the upper ring eclipse the 'short' bonds of the lower one. However, distortion of the inter-trimer interactions [*cf.* $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$] is insignificant here. Furthermore, it is apparent that the core of $(\mathbf{4})_6 \cdot 2\text{PhMe}$ is generally more compact than that of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$.

Stabilisation of the metal centre is assisted by cyclisation whereby, as in the previous structure, the α-N-centre donates electron density to the lithium centre, thus creating a strained four-membered ring system. Consequently the *intra*-monomer Li–O bond and not the *inter*-monomer one represents the *longer* of the two classes of observed lithium-oxygen linkage within either ring trimer. Furthermore, coordination of the α-N-centre dictates to a large extent the orientations both of the dialkylamine moiety and of the protected formyl group. Unlike the enantiomerically pure trimeric rings of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$, those observed in $(\mathbf{4})_6 \cdot 2\text{PhMe}$ contain both optical isomers in a 2 : 1 ratio. This can be clearly seen in Fig. 2(b), wherein C(21) and C(34A) (upper trimer ring) are (*S*)-stereocentres, with C(8A) being (*R*)-type. While substituents about the C(8A)–N(1A) bond are *anti*-disposed, those in the two (*S*)-monomers exhibit both *anti*-[about N(3)–C(21)] and *syn*-[about N(5A)–C(34A)] isomerisation. While simple inversion relates the six isomeric centres in the lower ring, the observation of *syn*-isomerism in $(\mathbf{4})_6 \cdot 2\text{PhMe}$ provides the first

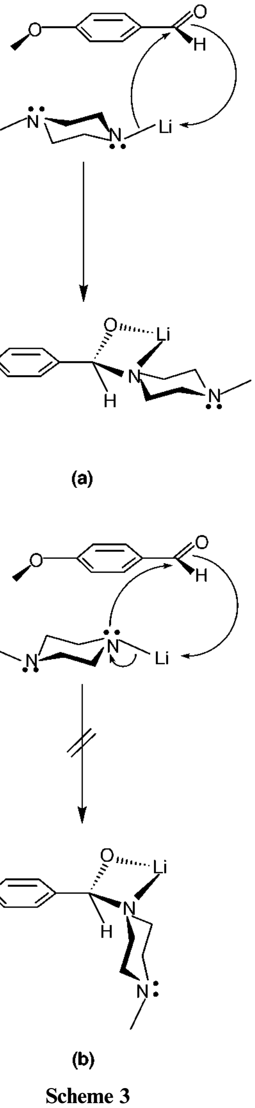


Scheme 2

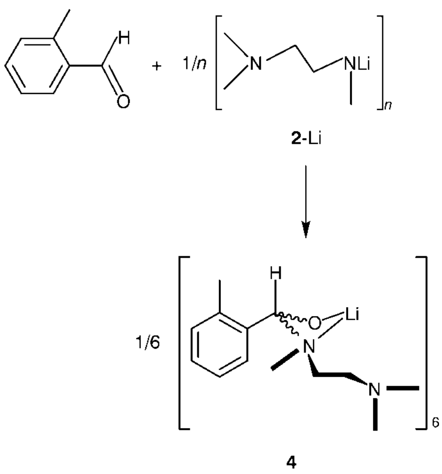
solid-state glimpse of the structural motif suggested for lithium (N,N,N'-trimethylethylenediamino)(2-methoxyphenyl) methoxide in solution.[9b]

Theoretical calculations

Ab initio molecular orbital (MO) calculations bear out the expectation that N–C–O–Li bonded *syn*-monomers will be nominally less stable than their *anti*-counterparts by virtue of the minimisation of steric interactions between the aromatic ring and dialkylamine moiety in the latter isomer. Hence, in spite of the replacement of these bulky organic residues with simpler groups, calculations suggest that *anti*-Me(H)C[N(Me) H]OLi is marginally preferred to its *syn*-analogue (Table 1). The ability of *hexameric* $(\mathbf{4})_6 \cdot 2\mathrm{PhMe}$ to incorporate *syn*-isomers in the solid state, whereas *tetrameric* α-amino lithium alkoxides include only *anti*-ones,[9] presumably reflects the



Scheme 3



Scheme 4

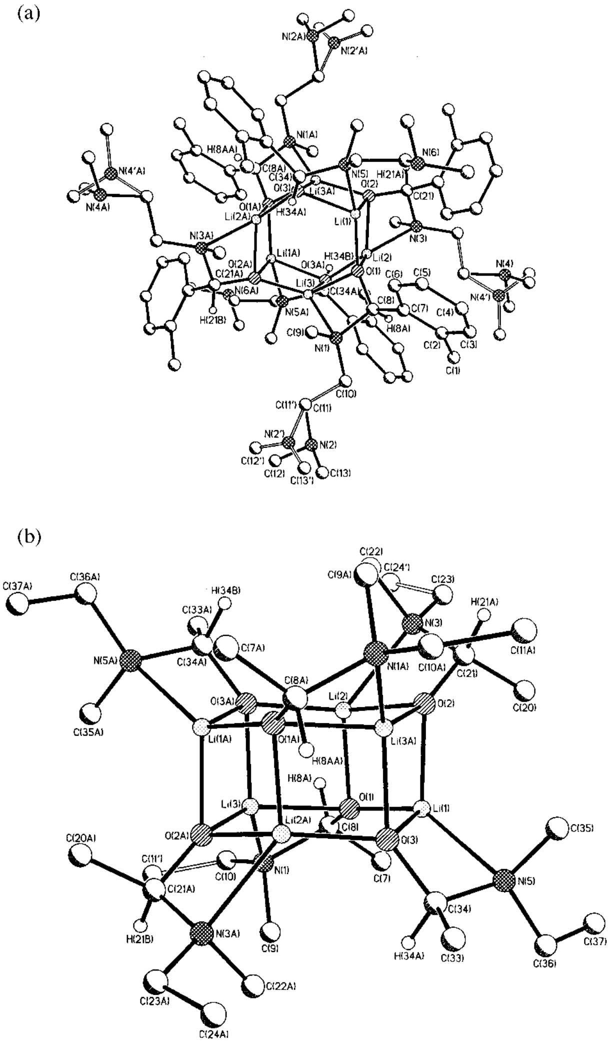
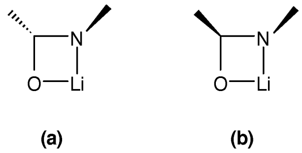


Fig. 2 (a) Molecular structure of $(\mathbf{4})_6 \cdot 2\mathrm{PhMe}$; hydrogen atoms (except the protected aldehyde hydrogen atoms) and the lattice toluene molecules have been omitted for clarity. (b) The $(\mathrm{LiO})_6$ core of $(\mathbf{4})_6 \cdot 2\mathrm{PhMe}$.

Table 1 Absolute (Abs.) and Relative (Rel.) energies of monomeric Me(H)C[N(Me)H]OLi calculated with the 6-31G* basis set



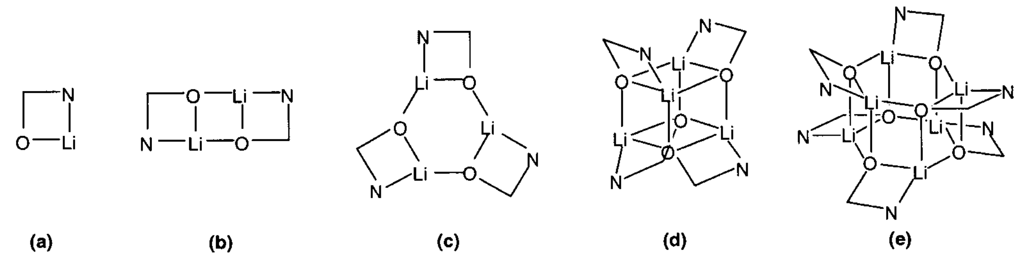
Configuration	Abs. energy/E_h	Rel. energy/ kcal mol^{-1}
(a) (*R*)-*anti*	−255.046845	0.0
(b) (*S*)-*syn*	−255.042536	2.7

greater favourability of minimising inter-monomer ligand interactions in the more crowded hexamer.

It was made desirable, given the wide variety of α-amino lithium alkoxide structures reported here and previously,[9] to probe theoretically the stability of these systems. Preliminary results on both the simple $[H_2C(NH_2)OLi]_n$ ($n = 1, 2, 3, 4, 6$) system (Table 2) and the more complex chiral $[Me(H)C(NH_2)OLi]_n$ ($n = 1, 2, 3, 4, 6$) system (Table 3) clearly show not only that aggregate stability, ΔH_{agg}, increases with *n*, but also that as the aggregation state is raised so the stabilisation energy *per monomer* increases by diminishing amounts.[18] Table 4 compares the structural parameters optimised with the 6-31G* basis set for the most stable $[H_2C(NH_2)OLi]_6$ and $[Me(H)C(NH_2)OLi]_6$ structures with those observed for $(\mathbf{3})_6 \cdot 2PhMe \cdot THF$ and $(\mathbf{4})_6 \cdot 2PhMe$.

Calculations (6-31G* basis set) on even the simplified structural motif $\{[H_2C(NH_2)OLi]_n\}$ demonstrate that the magnitude of the observed increments in $\Delta H_{agg}/n$ decrease as *n* is raised. As far as bonding parameters go it is clear that for $n = 6$ calculations are in reasonable agreement with both observed hexamers (Table 4). The calculated inter-trimer distance of 1.935 Å agrees well with the mean value of 1.941 Å observed for $(\mathbf{4})_6 \cdot 2PhMe$ while the remaining theoretical bond lengths show superior correlation with the structure of $(\mathbf{3})_6 \cdot 2PhMe \cdot THF$. Related calculations on the four possible hexamers [Table 3, structures (i)–(l)] of the more complex chiral analogue $[Me(H)C(NH_2)OLi]_6$, indicate optimum stability for the (*S*)-*exo*/(*S*)-*exo*/(*R*)-*endo* form [Table 3, structure (k)] (wherein chiral configurations quoted are for the three monomer units comprising the top trimeric ring of a double trimer stack motif viewed *in clockwise order* from *above* and are related to their counterparts in the lower ring by inversion). Readily apparent from Table 4 is the fact that the most stable calculated hexameric racemate not only demonstrates identical optical centres and orientation of the protected aldehyde protons as $(\mathbf{4})_6 \cdot 2PhMe$, but that bond distances compute remarkably accurately for inter-trimer interactions [calculated mean: 1.938 Å, observed mean for $(\mathbf{4})_6 \cdot 2PhMe$: 1.941 Å] but also reasonably accurately for intra-monomer Li–O and Li–N ones [calculated mean: 2.013 and 2.134 Å, observed mean for $(\mathbf{4})_6 \cdot 2PhMe$: 1.987 and 2.164 Å].

Table 2 Summary of calculations based on $[H_2C(NH_2)OLi]_n$ ($n = 1, 2, 3, 4$ 6) (1 kcal = 4.184 kJ) and mean geometric parameters (distances in Å, angles in °) for $[H_2C(NH_2)OLi]_n$ calculated with the 6-31G* basis set

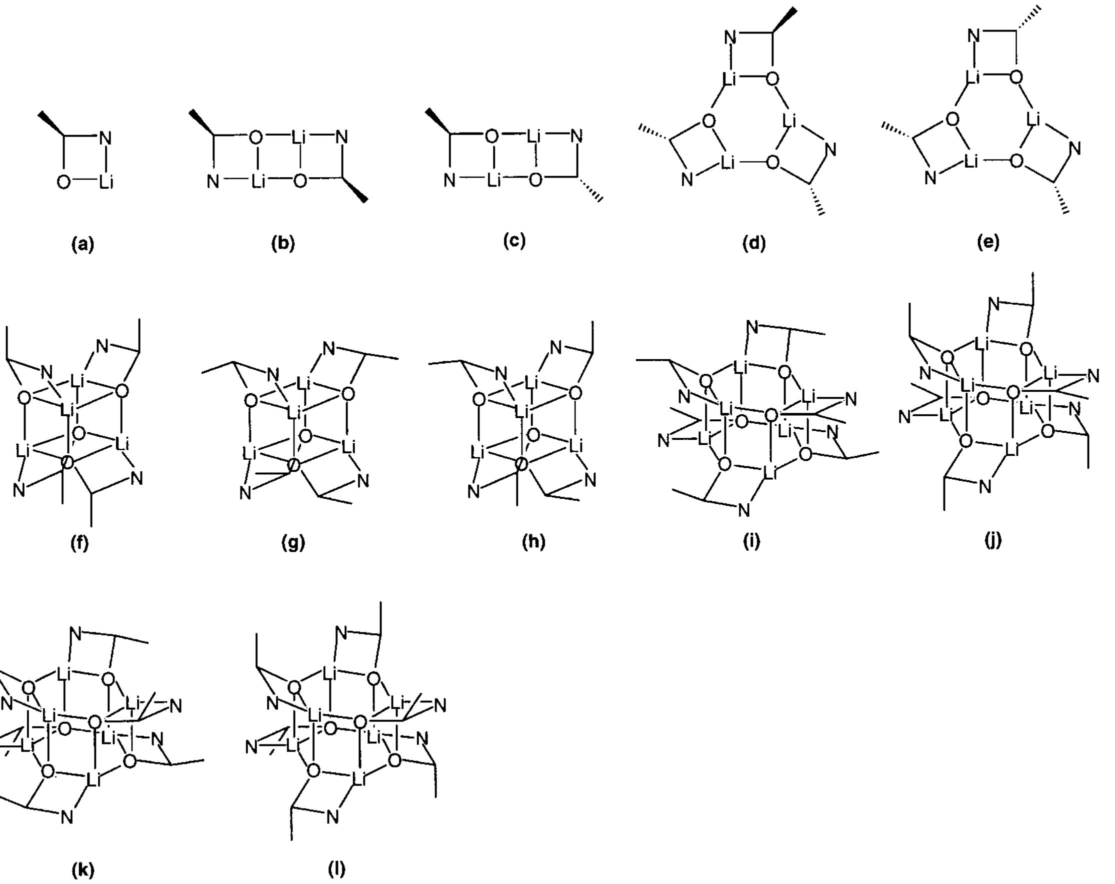


	6-31G basis set at SCF level			6-31G* basis set at SCF level		
n	Abs. energy/E_h	ΔH_{agg}/ kcal mol^{-1}	($\Delta H_{agg}/n$)/ kcal mol^{-1} monomer^{-1}	Abs. energy/E_h	ΔH_{agg}/ kcal mol^{-1}	($\Delta H_{agg}/n$)/ kcal mol^{-1} monomer^{-1}
(a) 1	−176.912568	0.0	0.0	−176.979098	0.0	0.0
(b) 2	−353.938922	71.4	35.7	−354.057943	62.6	31.3
(c) 3	−530.948862	132.6	44.2	−531.124275	117.1	39.0
(d) 4	−707.971107	201.3	50.3	−708.204488	180.8	45.2
(e) 6	−1061.989140	322.2	53.7	−1062.336447	289.8	48.3

	n				
	1 (a)	2 (b)	3 (c)	4 (d)	6 (e)
Li–O[a]	—	—	—	1.900	1.935
Li–O[b]	1.725	1.910	1.869	2.076	2.015
Li–O[c]	—	1.776	1.776	1.897	1.878
Li–N	2.017	2.110	2.127	2.110	2.139
Li–N–C[d]	78.4	83.0	82.7	87.3	85.1
Li–O–C[d]	95.0	95.3	97.2	92.7	93.5
N–Li–O[d]	77.0	70.0	70.6	67.3	67.6
N–C–O[d]	109.5	109.0	109.5	109.8	109.5
O–Li–O[e]	—	101.8	130.8	99.3	126.0
Li–O–Li[e]	—	78.2	109.2	80.3	111.9

[a] Inter-ring distance. [b] Intramonomer ('long') Li–O bond. [c] Intermonomer ('short') Li–O bond. [d] Within each NCOLi chelate. [e] Within each $(OLi)_n$ ($n = 2$ or 3) or $(OLi)_{n/2}$ ($n = 4$ or 6) ring.

Table 3 Summary of calculations based on $[Me(H)C(NH_2)OLi]_n$ (n = 1, 2, 3, 4, 6) and mean geometric parameters (distances in Å, angles in °) for the most stable aggregates of $[Me(H)C(NH_2)OLi]_n$ calculated with the 6–31G* basis set



(a) (b) (c) (d) (e)

(f) (g) (h) (i) (j)

(k) (l)

		6-31G basis set at SCF level			6-31G* basis set at SCF level		
	n	Abs. energy/E_h	ΔH_{agg}/ kcal mol^{-1}	$(\Delta H_{agg}/n)$/ kcal mol^{-1} monomer^{-1}	Abs. energy/E_h	ΔH_{agg}/ kcal mol^{-1}	$(\Delta H_{agg}/n)$/ kcal mol^{-1} monomer^{-1}
(a)	1	−215.940166	0.0	0.0	−216.021465	0.0	0.0
(b)	2	−431.992161	70.2	35.1	−432.141763	62.0	31.0
(c)	2	−431.992144	—	—	—	—	—
(d)	3	−648.027762	129.9	43.3	−648.249141	115.9	38.6
(e)	3	−648.027748	—	—	—	—	—
(f)	4[f]	−864.073853	—	—	—		
(g)	4[g]	−864.074935	—	—	—		
(h)	4[h]	−864.075126	197.3	49.3	−864.369839	178.2	44.5
(i)	6[i]	−1296.142528	—	—	—	—	—
(j)	6[j]	−1296.143783	—	—	—	—	—
(k)	6[k]	−1296.144025	315.9	52.6	−1296.583103	285.1	47.5
(l)	6[l]	−1296.143865	—	—	—	—	—

	n				
	1 (a)	2 (b)	3 (d)	4 (h)	6 (k)[m]
Li–O[a]	—	—	—	1.905	1.938
Li–O[b]	1.726	1.911	1.878	2.066	2.013
Li–O[c]	—	1.769	1.777	1.900	1.881
Li–N	2.011	2.107	2.128	2.107	2.134
Li–N–C[d]	78.9	83.9	82.8	87.8	85.8
Li–O–C[d]	95.2	95.9	96.8	93.0	94.2
N–Li–O[d]	76.8	69.9	69.5	67.1	67.3
N–C–O[d]	108.5	108.0	107.5	108.5	108.2
O–Li–O[e]	—	101.7	130.7	99.7	126.1
Li–O–Li[e]	—	78.3	109.3	79.9	111.8

[a–e] See Table 2 footnotes. [f] (*R*)-*endo*/(*R*)-*endo*. [g] (*S*)-*exo*/(*S*)-*exo*. [h] (*S*)-*exo*/(*R*)-*endo*. [i] (*S*)-*exo*/(*S*)-*exo*/(*S*)-*exo*. [j] (*R*)-*endo*/(*S*)-*exo*/(*R*)-*endo*. [k] (*S*)-*exo*/(*R*)-*endo*/(*S*)-*exo*. [l] (*R*)-*endo*/(*R*)-*endo*/(*R*)-*endo*. [m] The chiral and geometrical configurations quoted for n = 6 are for the three monomer units comprising the top trimeric ring of a double trimer stack motif viewed *in clockwise order from above*. They are related to their counterparts in the lower ring by inversion.

Table 4 Mean geometric parameters (distances in Å, angles in °) for $(\mathbf{3})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$ and $(\mathbf{4})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$ compared with the most stable $[\mathrm{H_2C(NH_2)OLi}]_6$ and $[\mathrm{Me(H)C(NH_2)OLi}]_6$ structures calculated with the 6-31G* basis set

	$(\mathbf{3})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$	$(\mathbf{4})_6\cdot2\mathrm{PhMe}$	$[\mathrm{H_2C(NH_2)OLi}]_6$	$[\mathrm{MeHC(NH_2)OLi}]_6$
Configuration[g]	(*R*)-*exo*/ (*R*)-*exo*/ (*R*)-*exo*	(*S*)-*exo-anti*/ (*S*)-*exo-syn*/ (*R*)-*endo-anti*	—	(*S*)-*exo*/ (*S*)-*exo*/ (*R*)-*endo*
Li–O[a]	1.890	1.941	1.935	1.938
Li–O[b]	2.039	1.987	2.015	2.013
Li–O[c]	1.887	1.871	1.878	1.881
Li–N	2.144	2.164	2.139	2.134
Li–N–C[d]	81.9	83.3	85.1	85.8
Li–O–C[d]	89.1	93.6	93.5	94.2
N–Li–O[d]	67.8	66.5	67.6	67.3
N–C–O[d]	107.9	107.0	109.5	108.2
O–Li–O[e]	120.7	124.1	126.0	126.1
Li–O–Li[e]	115.0	113.5	111.9	111.8
Sum[f]	707.1	712.8	713.7	713.7

[a–e] See Table 2 footnotes. [f] Sum of mean angles in $(\mathrm{OLi})_3$ ring. [g] See footnote *m* to Table 3.

In light of the observed correlation between the optical and *endo*-/*exo*-isomers in the structure of $(\mathbf{4})_6\cdot2\mathrm{PhMe}$ and the most stable calculated $[\mathrm{Me(H)C(NH_2)OLi}]_6$ model, a more complex set of aggregates based on $\{\mathrm{Me(H)C[N(Me)H]OLi}\}_6$ (introducing *syn*-/*anti*-isomerism into the calculational work) was probed. Calculations used the (*S*)-*exo*/(*S*)-*exo*/(*R*)-*endo* hexamer of $[\mathrm{Me(H)C(NH_2)OLi}]_6$ [Table 3, structure (k)], with simple substitution of a methyl group for a hydrogen atom making the amine asymmetric [Table 5, structures (a)–(h)]. Results are summarised in Table 5.

These calculations break the modelled hexamers up into two groups based on ΔH_{agg}, four of the eight having computed aggregation enthalpies in the range 278.3–279.1 kcal $\mathrm{mol^{-1}}$ [Table 5, structures (b), (c), (e), (g)], the remainder, with ΔH_{agg} values in the range 282.9–284.4 kcal $\mathrm{mol^{-1}}$ [Table 5, structures (a), (d), (f) and (h)], being more stable. Of these latter four structures, the (*S*)-*exo-anti*/(*S*)-*exo-syn*/(*R*)-*endo-anti* one [Table 5, structure (f)] correlates with the observed experimental structure of $(\mathbf{4})_6\cdot2\mathrm{PhMe}$ (Table 6).

There is an overall pleasing agreement between the bond lengths and angles of the theoretical $\{\mathrm{Me(H)C[N(Me)H]OLi}\}_6$ aggregate [Table 5, structure (f)] and the corresponding experimental values of $(\mathbf{4})_6\cdot2\mathrm{PhMe}$ (Table 6). This is especially true when comparing the bond distances in the hexamer. The theoretical values confirm that the shortest Li–O bond lengths (1.883–1.888 Å) are those which interconnect the trimer rings while the longest such bond distances are present at the interface of the trimer and the N–C–O–Li chelate (1.999–2.022 Å). There are some small differences between the two sets of data, most noticeably in the values of the bond angles of the $(\mathrm{LiO})_6$ trimer rings. These discrepencies are presumably due to greater steric effects in the experimental structure not being mimicked in the simplified theoretical model.

Conclusion

The reactions of lithium *N*-methylpiperazide, **1**-Li, and lithium *N*,*N*,*N*′-trimethylethylenediamide, **2**-Li, with 4-methoxybenzaldehyde and 2-methylbenzaldehyde respectively afford the corresponding chiral α-amino lithium alkoxides, $(\mathbf{3})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$ and $(\mathbf{4})_6\cdot2\mathrm{PhMe}$. In the solid state these complexes have hexameric structures with $(\mathrm{LiO})_6$ cores based on two stacked trimeric rings. In both instances the bis(amino) moieties mono-coordinate the metal centres *via* their α-N-centres, affording stable, four-membered α-N–C–O–Li rings. For $(\mathbf{3})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$ this is due to the orientation of the δ-N-centre lone pair away from the metal centre to which the α-N-atom coordinates, a consequence of utilising a heterocyclic lithium amide (**1**-Li) in the reaction. Surprisingly, in light of previous results,[9b,10] a similar motif is observed for $(\mathbf{4})_6\cdot2\mathrm{PhMe}$ in spite of the expected availability of the δ-$\mathrm{NMe_2}$ group for bonding.

Ab initio MO calculations usefully probe the structures, showing that aggregate stability, ΔH_{agg}, increases with *n*, and also that as the degree of aggregation is raised so too is the stabilisation energy *per monomer*. However, the extent to which ΔH_{agg} increases is found to diminish as the aggregates get bigger. Extensive calculations based on hexameric aggregates of varying complexity point to the stability of the (*S*)-*exo*/(*S*)-*exo*/(*R*)-*endo* form of $[\mathrm{Me(H)C(NH_2)OLi}]_6$. Finally, there is good general agreement between the experimental bond parameters of $(\mathbf{4})_6\cdot2\mathrm{PhMe}$ and the corresponding values computed for the theoretical $\{\mathrm{Me(H)C[N(Me)H]OLi}\}_6$ aggregate.

Experimental

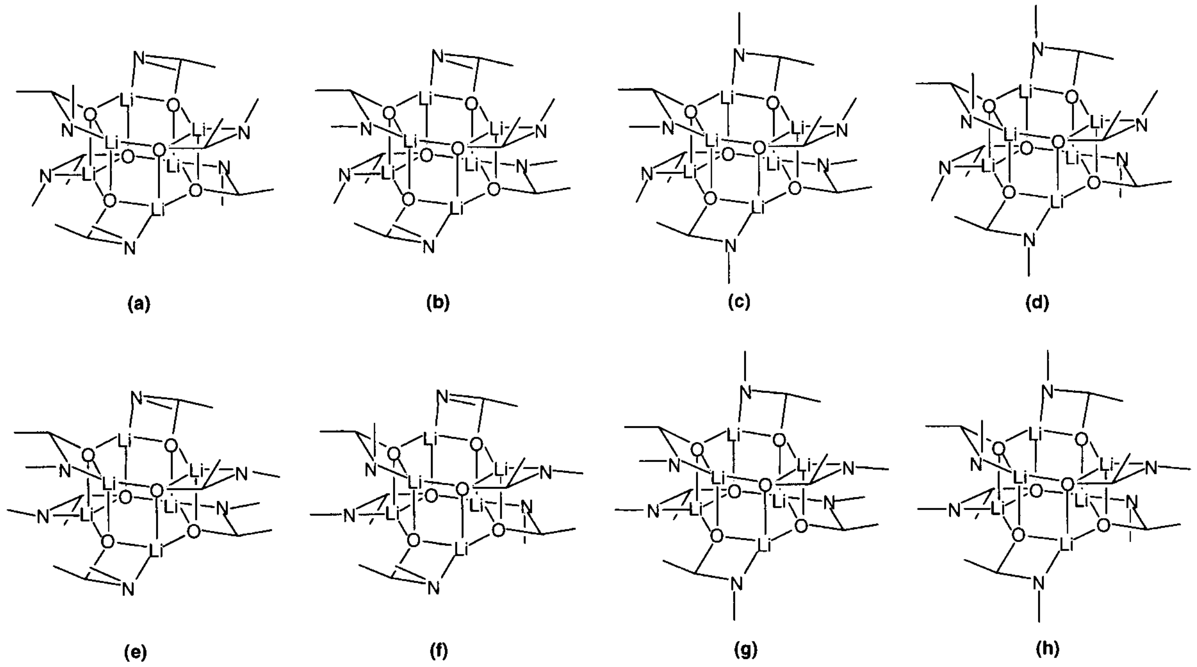
Synthesis of $(\mathbf{3})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$

$\mathrm{Bu^nLi}$ (1.88 ml, 1.6 M in hexanes, 3.0 mmol) was added to a mixture of *N*-methylpiperazine (0.33 ml, 3.0 mmol) and PMDETA (0.63 ml, 3.0 mmol) in 3 : 1 toluene–THF (12 : 4 ml) under nitrogen at −78°C. The resultant yellow solution was stirred for 10 min at −78°C whereupon 4-methoxybenzaldehyde (0.36 ml, 3.0 mmol) was added. After a further 10 min at this temperature the solution was allowed to warm to room temperature, yielding a white suspension. A yellow solution was obtained on refluxing, and subsequent storage at room temperature for 12 h afforded rhombohedral *and* hexagonal crystals of $(\mathbf{3})_6\cdot2\mathrm{PhMe}\cdot\mathrm{THF}$ which could be mechanically separated for the purpose of analysis, mp 255–257°C, yield 85% (51% rhombohedral, 34% hexagonal). Found: C, 66.12; H, 7.89; N, 9.56. Calc. for $\mathrm{C_{96}H_{138}Li_6N_{12}O_{13}}$: C, 67.45; H, 8.10; N, 9.84%. ^{1}H NMR spectroscopy (250.133 MHz, $[^2\mathrm{H_6}]$benzene), δ 7.52 (d, 12H, Ar, $^3J_{\mathrm{HH}} = 8.35$ Hz), 7.18 (d, 12H, Ar, $^3J_{\mathrm{HH}} = 8.43$ Hz), 6.96–6.88 (m, 5H, $\mathrm{C_6\underline{H}_5CH_3}$), 5.97–5.53 [m, 6H, $\mathrm{ArC(\underline{H})(O)N}$], 3.61 (m, 4H, THF), 3.50 (s, 3H, $\mathrm{OCH_3}$), 3.49–3.44 (m, 12H, $\mathrm{CH_2}$), 2.13 [s, 36H, $\mathrm{N(CH_3)_2}$], 2.17 (s, 3H, $\mathrm{C_6H_5C\underline{H}_3}$), 2.04 (br, 12H, $\mathrm{CH_2}$), 2.00 (br, 18H, $\mathrm{NCH_3}$), 1.45 (m, 4H, THF).

Synthesis of $(\mathbf{4})_6\cdot2\mathrm{PhMe}$

$\mathrm{Bu^nLi}$ (1.88 ml, 1.6 M in hexanes, 3.0 mmol) was added to *N*,*N*,*N*′-trimethylethylenediaminine (0.38 ml, 3.0 mmol) in 6 : 1 toluene–hexane (3:0.5 ml) at −78°C under nitrogen. After

Table 5 Summary of energies calculated for aggregates of $\{Me(H)C[N(Me)H]OLi\}_6$ {based on the most stable structure observed for theoretically modelled $[Me(H)C(NH_2)OLi]_n$} with the 6-31G* basis set



Configuration	Abs. energy/E_h	ΔH_{agg}/kcal mol^{-1}	($\Delta H_{agg}/n$)/kcal mol^{-1} monomer^{-1}
(*S*)-*exo-anti*$^{(a)}$ (*S*)-*exo-syn* (*R*)-*endo-syn*	−1530.732039	282.9	47.2
(*S*)-*exo-syn*$^{(b)}$ (*S*)-*exo-syn* (*R*)-*endo-syn*	−1530.724586	278.3	46.4
(*S*)-*exo-syn*$^{(c)}$ (*S*)-*exo-anti* (*R*)-*endo-syn*	−1530.725014	278.5	46.4
(*S*)-*exo-anti*$^{(d)}$ (*S*)-*exo-anti* (*R*)-*endo-syn*	−1530.734012	284.4	47.4
(*S*)-*exo-syn*$^{(e)}$ (*S*)-*exo-syn* (*R*)-*endo-anti*	−1530.725954	279.1	46.5
(*S*)-*exo-anti*$^{(f)}$ (*S*)-*exo-syn* (*R*)-*endo-anti*	−1530.732867	284.3	47.4
(*S*)-*exo-syn*$^{(g)}$ (*S*)-*exo-anti* (*R*)-*endo-anti*	−1530.725871	279.1	46.5
(*S*)-*exo-anti*$^{(h)}$ (*S*)-*exo-anti* (*R*)-*endo-anti*	−1530.734359	284.4	47.4

stirring for 10 min, 2-methylbenzaldehyde (0.35 ml, 3.0 mmol) was added. After a further 10 min at this temperature the solution was allowed to warm to room temperature, yielding a white suspension which dissolved on gentle heating. Storage of the resultant yellow solution for 12 h at room temperature afforded clear, rectangular crystals of $(\mathbf{4})_6 \cdot 2PhMe$, mp 108–110 °C, yield 67%. Found: C, 69.48; H, 9.86; N, 10.25. Calc. for $C_{92}H_{142}Li_6N_{12}O_6$: C, 71.13; H, 9.15; N, 10.82%. ^1H NMR spectroscopy (500.128 MHz, [$^2H_6$]benzene), δ 8.14 (d, 3H, Ar, $^3J_{HH} = 7.66$ Hz), 8.04 (d, 3H, Ar, $^3J_{HH} = 7.47$ Hz), 7.21 (d, 3H, Ar, $^3J_{HH} = 7.70$ Hz), 7.18–7.01 (m, 5H, $C_6\underline{H}_5CH_3$), 7.11 (d, 3H, Ar, $^3J_{HH} = 7.57$ Hz), 6.05–5.68 [m, 3H, ArC($\underline{H}$)(O)N], 2.61–2.52 (m, 9H, 2-CH_3), 2.49–2.36 (m, 12H, CH_2), 2.20 (s, 9H, NCH_3), 2.14 [s, 18H, $N(CH_3)_2$], 2.11 (s, 3H, $C_6H_5C\underline{H}_3$). ^{13}C NMR spectroscopy (100.614 MHz, d_6-benzene), δ 137.9 (1-/2-Ar), 134.8 (1-/2-Ar), 130.4, 129.3, 128.6, 126.8, 126.3, 125.7, 125.5 (Ar/$\underline{C}_6H_5CH_3$), 90.1, 89.7 [Ar$\underline{C}$(H)(O)N], 59.5–58.8 (m, CH_2), 52.9–50.3 (m, CH_2), 47.0–45.6 [m, $N(CH_3)_2$], 21.4 ($C_6H_5\underline{C}H_3$), 20.4 (m, NCH_3).

X-Ray crystallography

Crystals of $(\mathbf{3})_6 \cdot 2PhMe \cdot THF$ and $(\mathbf{4})_6 \cdot 2PhMe$ were mounted directly into the cold stream of an Oxford Cryostream crystal cooling apparatus, installed on a Stoe-Siemens four-circle diffractometer, using perfluoropolyether oil. Essential crystallographic details are given in Table 7. Data were recorded using the ω–θ scan technique. Both structures were solved by direct methods[19] and from subsequent Fourier difference techniques, and refined by full-matrix least squares based on F^2.[20] Hydrogen atoms were placed in idealised positions and allowed to ride on the relevant carbon atom; methyl H-atoms were

Table 6 Comparison of bond lengths and angles (distances in Å, angles in °) for $(\mathbf{4})_6 \cdot 2\text{PhMe}$ and the $\{\text{Me(H)C[N(Me)H]OLi}\}_6$ model with the same structure [Table 5, structure (f)] calculated with the 6-31G* basis set

	(*S*)-*exo*-*syn*		(*S*)-*exo*-*anti*		(*R*)-*endo*-*anti*	
	$(\mathbf{4})_6 \cdot 2\text{PhMe}$	$[\text{MeHC(NMeH)OLi}]_6$	$(\mathbf{4})_6 \cdot 2\text{PhMe}$	$[\text{MeHC(NMeH)OLi}]_6$	$(\mathbf{4})_6 \cdot 2\text{PhMe}$	$[\text{MeHC(NMeH)OLi}]_6$
Li–O[a]	1.928(13)	1.925	1.951(13)	1.935	1.944(14)	1.943
Li–O[b]	1.961(14)	2.022	2.033(13)	2.004	1.996(13)	1.999
Li–O[c]	1.875(13)	1.887	1.879(14)	1.887	1.858(12)	1.883
Li–N	2.178(13)	2.168	2.19(2)	2.151	2.123(13)	2.159
Li-N-C[d]	84.9(5)	85.6	81.5(5)	84.6	83.6(5)	84.5
Li-O-C[d]	96.9(6)	94.8	91.9(5)	93.8	92.1(5)	94.2
N–Li–O[d]	68.3(5)	65.9	67.4(4)	67.0	68.4(4)	67.7
N–C–O[d]	106.6(6)	106.9	107.3(6)	108.1	107.1(6)	109.3
O-Li-O[e]	125.8(6)	125.5	113.5(7)	126.4	132.9(8)	124.0
Li-O-Li[e]	104.1(6)	113.0	121.3(6)	110.6	115.2(6)	112.8

[a–e] See Table 2 footnotes.

refined with an isotropic displacement parameter 1.5 times that of associated carbon and other H-atoms with a displacement parameter of 1.2 times. In both structural refinements the atoms within the lithium complexes were refined with anisotropic displacement parameters, while those of the solvent were refined with isotropic displacement parameters. In the structure of $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$, each asymmetric unit contained half a THF molecule [C(300)–C(304)] that was refined with occupancies fixed at 50%, and a whole toluene molecule that was disordered over the sites C(100)–C(106) and C(200)–C(206); each site was assigned 50% occupancy. In the structure of $(\mathbf{4})_6 \cdot 2\text{PhMe}$ the N(2), C(11), C(12), C(13) and N(4), C(24), C(25), C(26) ligands showed positional disorder over two sites. These sites were refined with partial occupancies summing to unity; 87 : 13 for the N(2)–C(13)/N(2′)–C(13′) groups and 49 : 51 for the N(4)–C(26)/N(4′)–C(26′) ones. Bond parameters and displacement parameters were restrained to the chemically reasonable by use of SAME and SADI instructions (SHELXL-93). Each asymmetric unit in $(\mathbf{4})_6 \cdot 2\text{PhMe}$ contained a toluene solvent molecule that was disordered over two sites [C(201)–C(207) and C(301)–C(307)] and these sites were all refined with half occupancies. In the final cycles of refinement a weighting scheme of the form $\omega = 1/[\sigma^2(F_o^2) + (xP)^2 + yP]$ where $P = (F_o^2 + 2F_c^2)/3$. Refinement continued until convergence was reached. Final Fourier difference syntheses showed no remaining regions of significant electron density.

Table 7 Cyrstallographic data for $(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$ and $(\mathbf{4})_6 \cdot 2\text{PhMe}$

	$(\mathbf{3})_6 \cdot 2\text{PhMe} \cdot \text{THF}$	$(\mathbf{4})_6 \cdot 2\text{PhMe}$
Formula	$C_{96}H_{138}Li_6N_{12}O_{13}$	$C_{92}H_{142}Li_6N_{12}O_6$
M_r	1709.82	1553.82
Space group	$P\bar{1}$	$P\bar{1}$
a/Å	12.465(14)	12.367(10)
b/Å	15.21(2)	15.022(11)
c/Å	15.227(13)	15.256(11)
α/°	92.99(7)	108.09(5)
β/°	107.62(7)	112.31(6)
γ/°	114.08(7)	101.34(6)
V/Å^3	2461(5)	2327(3)
Z	1	1
D_c/g cm^{-3}	1.154	1.109
Crystal size/mm	0.30 × 0.30 × 0.10	0.20 × 0.15 × 0.10
Radiation (λ/Å)	Mo-Kα (0.71073)	Mo-Kα (0.71073)
μ/mm^{-1}	0.076	0.068
F(000)	920	844
T/K	153(2)	153(2)
Scan mode	ω–θ	ω–θ
2θ range/°	8.04–50.00	7.06–45.00
Measured refl.	11107	6450
Unique refl.	8620	6057
R_{int}	0.0371	0.3907
Refl. with $I > 2\sigma(I)$	8599	6035
Final $R(F)$, $wR(F^2)$	0.0578, 0.1677	0.1063, 0.2933
Weighting scheme x, y	0.0685, 1.8210	0.0411, 12.3339
Goodness-of-fit	1.039	1.099
Max. peak, hole/e Å^{-3}	0.512, −0.368	0.416, −0.330

CCDC reference number 440/105.

See http://www.rsc.org/suppdata/nj/1999/499/ for crystallographic files in .cif format.

Theoretical calculations

Ab initio calculations using the GAMESS[21] and GAUSSIAN 94[22] computer programs were done on $[\text{H}_2\text{C(NH}_2\text{)OLi}]_n$ and on $[\text{Me(H)C(NH}_2\text{)OLi}]_n$ ($n = 1, 2, 3, 4, 6$). Initially calculations used the 6-31G basis set[23] at the SCF level and the resulting geometries were subjected to a frequency analysis to verify the presence of a local minimum. The most stable geometries up to the hexamer were then reoptimised with the 6-31G* basis set.[23] These parameters[23] were also employed to model *syn*-/*anti*-isomerism in $\{\text{Me(H)C[N(Me)H]OLi}\}_6$, the chiral and *endo*-/*exo*-configuration of which was based on the theoretically most stable optimised structure for $[\text{Me(H)C(NH}_2\text{)OLi}]_6$.

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